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No. ——

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1981

Undetermined quantities of various articles of drug . . . EQUIDANTIN . . .,

PERFORMANCE PRODUCTS, INC.,

Petitioner,

vs.

UNITED STATES OF AMERICA,

Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE EIGHTH CIRCUIT

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QUESTIONS PRESENTED FOR REVIEW

1. Does the Eighth Circuit's decision in this case conflict with the decision of the Fifth Circuit in *United States* v. *Generix Drug Corp.*, 654 F. 2d 1114 (5th Cir.), *cert. granted*, 102 S. Ct. 1610 (1982), and improperly construe the applicable statutory provisions?

2. Should "new animal drug" in 21 U.S.C. § 321(w) (1976) be defined according to the analysis of the Fifth Circuit in *United States* v. *Generix Drug Corp.*, 654 F. 2d 1114 (5th Cir.), *cert. granted*, 102 S. Ct. 1610 (1982), defining "new drug" in 21 U.S.C. § 321(p) (1976), or according to the conflicting analysis of the Second Circuit in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F. 2d 795 (2d Cir. 1980)?

3. Was it reversible error for the Eighth Circuit to affirm the district court's judgment that the seized article of drug was a "new animal drug," according to 21 U.S.C. § 321(w) (1976), in light of the Fifth Circuit's decision in *United States* v. *Generix Drug Corp.*, 654 F. 2d 1114 (5th Cir.), *cert. granted*, 102 S. Ct. 1610 (1982)?

TABLE OF CONTENTS

	Page
QUESTIONS PRESENTED	i
TABLE OF CONTENTS	iii
TABLE OF AUTHORITIES	iv
OPINIONS BELOW	2
JURISDICTION	2
STATUTES INVOLVED	2
STATEMENT OF THE CASE	3
REASONS FOR GRANTING THE WRIT	5
CONCLUSION	8

APPENDIX A

Opinion—United States Court of Appeals for the Eighth Circuit	A1
Judgment—United States District Court for the Eastern District of Missouri	A18
Findings of Fact and Conclusions of Law—United States District Court for the Eastern District of Missouri	A19

APPENDIX B

21 U.S.C. § 321(p) (1976)	B1
21 U.S.C. § 321(w) (1976)	B2

TABLE OF AUTHORITIES

Cases	Page
Premo Pharmaceutical Laboratories v. *United States*, 629 F. 2d 795 (2d Cir. 1980)	4, 5, 7
United States v. *Articles of Drug (Lannett)*, 585 F. 2d 575 (3d Cir. 1978)	7
United States v. *Generix Drug Corp.*, 654 F. 2d 1114 (5th Cir.), *cert. granted*, 102 S. Ct. 1610 (1982)	4, 5, 6
United States Statutes	
21 U.S.C. § 321(p) (1976)	2, 5
21 U.S.C. § 321(w) (1976)	2, 3, 5

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PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE EIGHTH CIRCUIT

The petitioner, Performance Products, Inc[1]., respectfully requests that a writ of certiorari issue to review the judgment and opinion of the United States Court of Appeals for the Eighth Circuit entered April 15, 1982.

1. Performance Products, Inc. is an independent corporation without a parent corporation or subsidiaries.

OPINIONS BELOW

The opinion of the court of appeals, not yet published, appears in Appendix A at pages 1-17 [hereinafter Appendices will be cited in parentheses as A or B with page numbers]. The judgment, findings of fact, and conclusions of law of the district court is reported at [New Matters] FOOD DRUG COSM. L. REP. (CCH) ¶38,120 (E.D. Mo. May 29, 1981) (A18-24).

JURISDICTION

The judgment of the court of appeals was entered on April 15, 1982. This petition was filed within 90 days of that date. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1) (1976).

STATUTES INVOLVED*

21 U.S.C. § 321(p) (1976)
21 U.S.C. § 321(w) (1976)

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* The texts of both statutes appear in Appendix B.

STATEMENT OF THE CASE

This petition, filed by Performance Products, Inc. [hereinafter Performance] is based upon a seizure action brought by the United States of America under the Federal Food, Drug, and Cosmetic Act [hereinafter the Act], 21 U.S.C. § 301 *et seq.* (1976), against the article of drug Equidantin, a brand of nitrofurantoin oral suspension. The subject matter jurisdiction of the District Court was premised upon 21 U.S.C. § 334 (1976) and 28 U.S.C. § 1345 (1976).

Performance has manufactured Equidantin brand of nitrofurantoin oral suspension since 1970. It is intended for use in the treatment of equine tracheopharyngitis ("race track cough") and bacterial urinary tract infections. The active ingredient in Equidantin is nitrofurantoin, which is also the active ingredient in a drug approved by the Food and Drug Administration [hereinafter FDA], Dantafur. Equidantin and Dantafur both contain the same amount of nitrofurantoin per dosage unit, and the inactive ingredients in the two drugs are different.

A complaint for forfeiture was filed on July 25, 1979 against the defendant article of drug. The United States alleged that the seized articles were adulterated, according to 21 U.S.C. § 351 (a)(5) (1976), because they were "new animal drugs," according to 21 U.S.C. § 321(w) (1976), for which there was no approved "new animal drug" application in effect. Performance maintained that the articles were not "new animal drugs" because the product was generally recognized as safe and effective for its intended uses. Performance also maintained that the Government had failed to establish by a preponderance of the evidence that the seized articles were adulterated.

The seizure action was tried without a jury, and on May 29, 1981 the district court ruled that the seized articles

were "new animal drugs" for which no approval was in effect and, therefore, were adulterated. The articles were condemned and forfeited by an order dated July 2, 1981, which was stayed pending appeal. Performance appealed the judgment on July 28, 1981 to the Court of Appeals for the Eighth Circuit.

On appeal, Performance asserted that nitrofurantoin oral suspension at the dosage levels and for the indications prescribed and recommended in the labeling for Equidantin was not a "new animal drug." The bases of its assertion were that Equidantin's active ingredient, nitrofurantoin, was generally recognized as safe and effective for its prescribed uses, and that the United States had failed to prove by a preponderance of the evidence that it was a "new animal drug." Performance also contended that the Fifth Circuit's decision in *United States* v. *Generix Drug Corp.*, 654 F. 2d 1114 (5th Cir.), *cert. granted*, 102 S. Ct. 1610 (1982), was correct and supported its position that the term "new animal drug" applies only to a drug's active ingredients and that the Second Circuit's conflicting analysis in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F. 2d 795 (2d Cir. 1980), was unsupported by the language of the statute or its legislative history.

In affirming the district court, the Eighth Circuit held that the testimony of the experts proffered by the Government established that Equidantin was not generally recognized as safe and effective. However, the testimony of the Government's experts relied, to a significant extent, on the lack of bioavailability studies for the seized drug. The court of appeals held that, even under the *Generix* test in which the active ingredient is determinative of "new drug" status, nitrofurantoin was not generally recognized as safe and effective. Therefore, the court of appeals con-

cluded that it was not required to reach the issue of whether *Generix* or *Premo* was the correct standard for defining "new animal drug" status for the seized articles.

Performance asserted at oral argument that the issue of bioavailability being an attribute of a "new animal drug" so pervaded the proceeding and testimony in the district court that the issue must be addressed as part of the ultimate resolution of the case, and it asserts this point in support of its petition.

REASONS FOR GRANTING THE WRIT

Petitioner in the instant case raises issues of law which are presently before this Court in *United States* v. *Generix Drug Corp.*, 654 F. 2d 1114 (5th Cir.), *cert. granted*, 102 S. Ct. 1610 (1982). The principal issue in the instant proceeding is whether the article seized is a "new animal drug" within the meaning of 21 U.S.C. § 321(w) (1976) (B2). This determination requires an interpretation of the definition of "new animal drug" in conjunction with the interpretation of the definition of "new drug" found in 21 U.S.C. § 321(p) (1976) (B1), which is the subject of conflicting interpretations by the Fifth Circuit in *Generix* and the Second Circuit in *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F. 2d 795 (2d Cir. 1980)[2].

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2. Both *Generix* and *Premo* concern the definition of a "new drug" contained in 21 U.S.C. § 321(p) (1976), which applies to human drugs. The statutory definition relevant to this proceeding, for "new animal drugs," is 21 U.S.C. § 321(w) (1976). The applicable language of each is virtually identical and, in fact, prior to 1968, the year when § 321(w) was added to the statute, animal drugs and human drugs were all subject to the definition set forth in § 321(p). Additionally, the other relevant statutory provisions applicable to new human and animal drugs are virtually identical.

Although the Eighth Circuit in its decision expressly stated that it was not required to address the issues upon which the Second and Fifth Circuits disagreed, its ruling implicitly adopted the *Premo* rationale that bioavailability is an attribute of a "new animal drug" by its acceptance of and reliance upon the expert testimony presented by the Government. Furthermore, the relevance of bioavailability to "new animal drug" status was a key issue raised by Performance at trial.

Bioavailability is the study of the rate and extent of drug absorption (A3). Testimony on bioavailability had a decisive impact on this proceeding. The importance of and reliance placed upon the issue of bioavailability is manifested by the fact that the two Government witnesses testifying on the effectiveness and safety of nitrofurantoin suspensions both relied upon the absence of bioavailability data to support in their opinions. Also, the third witness, Dr. Meyer, did not testify to the safety and efficacy of the seized product; rather, his testimony was completely addressed to the matter of bioavailability (A14-15). Performance objected to all testimony relating to bioavailability. The district court overruled Performance's objections, admitted the testimony, and relied on it, in part, as a basis for its decision (A3-4, A14-15).

The relevancy of bioavailability to "new drug" status has been directly addressed by two courts of appeal and in the dicta of a third. In *Generix*, 654 F. 2d at 1119-20, the Fifth Circuit stated:

> It may well be good public policy to regulate the bioavailability and bioequivalence through the NDA or some equivalent process. However, we have found that the statutory language and history of the Food, Drug and Cosmetic Act does not require such approval. The judicial branch may not legislate to fill perceived voids in public policy.

The Second Circuit in *Premo*, 629 F. 2d at 805, adopted a different analysis of the importance of bioavailability, stating:

> On the other hand, later developed "me-too" products such as Insulase are required to apply for FDA approval for the undisputed reason that a difference in inactive ingredients, as exists here, when combined with the active ingredient, can affect the safety and effectiveness of the drug product (footnote omitted).

In *United States* v. *Articles of Drug* (*Lannett*), 585 F. 2d 575, 582 (3d Cir. 1978), the Third Circuit addressed the issue of bioavailability in dicta, stating:

> . . . bioavailability, bioequivalence, and other quality control tests are irrelevant as to safety and efficacy.

Performance asserted in its appeal that the correct interpretation of the statute, was the one adopted by the Fifth Circuit because it is supported by the legislative history and statutory language. Further, this was the basis for the objections to the introduction and consideration of bioavailability testimony upon the ground that it is not an attribute of a "new animal drug." The Eighth Circuit did not expressly discuss Performance's challenge to the admission of bioavailability testimony. However, it did indicate that the testimony at trial supported the district court's finding that the seized article of drug was not generally recognized as safe and effective, and it described the testimony of the Government's witnesses, including a reference to testimony on bioavailability (A14-15).

The fact that bioavailability was an important issue in the proceeding, one inextricably involved in the final determination of "new animal drug" status, is manifest in the court of appeals' decision. The issue of bioavailability as an attribute of a new drug pervades the proceedings below and is one on which the circuits disagree. The

relevance of bioavailability to "new drug" and "new animal drug" status is an important matter and one which has a significant bearing on the marketing of drugs under the Act. Therefore, its resolution will have far-reaching consequences and is deserving of this Court's review.

Petitioner submits that this issue is one which will be addressed by the parties in *Generix* and that the present case should be heard and ruled upon concurrently.

CONCLUSION

For the reasons stated above, a writ of certiorari should issue to review the judgment and opinion of the Court of Appeals for the Eighth Circuit.

Respectfully submitted,

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UNITED STATES COURT OF APPEALS
FOR THE EIGHTH CIRCUIT

No. 81-1793

UNITED STATES OF AMERICA,
Appellee,

v.

Undetermined quantities of various articles of drug . . .
EQUIDANTIN NITROFURANTOIN SUSPENSION . . .,
PERFORMANCE PRODUCTS, INC.,
Appellant.

Appeal from the United States District Court for the Eastern District of Missouri.

Submitted: February 9, 1982

Filed: April 15, 1982

Before LAY, Chief Judge, McMILLIAN, Circuit Judge, and OVERTON,* District Judge.

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* The Honorable William R. Overton, United States District Judge for the Eastern District of Arkansas, sitting by designation.

McMILLIAN, Circuit Judge.

Performance Products, Inc. (Performance) appeals from a final judgment entered in the District Court[1] for the Eastern District of Missouri condemning as adulterated and seizing certain quantities of an animal drug called Equidantin and other materials used in its manufacture. For reversal Performance argues that Equidantin is not a "new animal drug" within the meaning of 21 U.S.C. § 321(w), and thus not subject to premarketing clearance by the Food and Drug Administration (FDA) under 21 U.S.C. § 360b(b), because (1) Equidantin is generally recognized as safe and effective and (2) Equidantin is a generic drug or copy of Dantafur, a drug that has been approved by the FDA. For the reasons discussed below, we affirm the judgment of the district court.

Performance is the manufacturer of Equidantin. Equidantin has been on the market since 1970 and is intended for use in the treatment of equine tracheopharyngitis ("race track cough") and equine urinary tract bacterial infections. The active ingredient in Equidantin is nitrofurantoin, which is also the active ingredient in Dantafur, an FDA-approved drug manufactured and marketed by Norwich-Eaton Pharmaceuticals. Equidantin and Dantafur contain the same amount of nitrofurantoin per dosage unit. However, the inactive ingredients in the two drugs are different. Dantafur contains alcohol among other inactive ingredients. According to the government's evidence, Equidantin contains the following inactive ingredients: xantham gum (a suspending agent), magnesium aluminum silicate (a suspending agent), potassium sorbate (a preservative), propylene glycol, citric acid (a buffer),

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1. The Honorable James H. Meredith, United States Senior District Judge for the Eastern District of Missouri.

anethole (a flavoring agent), sodium saccharin (a flavoring agent), vanillin, and deionized water.

Equidantin is a generic drug or copy (a "me-too" version) of Dantafur, the FDA-approved "brand name" or pioneer drug. A generic drug contains the same active ingredient or "incipient" as an FDA-approved pioneer drug but may contain different inactive ingredients or "excipients." The manufacturing techniques used by each manufacturer may also differ. It is not disputed that differences in the manufacturing process and variations in the inactive ingredients may affect a drug's "bioavailability." Bioavailability is "the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action." 21 C.F.R. § 320.1(a) (1981).

> If there is no significant difference between the rate and extent of absorption of two drugs administered at the same molar dose of therapeutic moiety under similar experimental conditions, the drugs are said to be bioequivalent. *See* 21 C.F.R. § 320.1(e) (1980). When two different drug products are to be used interchangeably in the treatment of illness, it can be critical that the drug products are bioequivalent—that is, that there be no significant difference in the products' bioavailability. A drug that is less bioavailable than that for which it is substituted will deliver less of its active ingredient than expected; a drug that is more bioavailable than that which it replaces presents the danger of overdosage.

United States v. *Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 962-63 (D.N.J. 1981) (*Premo II*) (footnote omitted) (excellent discussion of factors which may affect bioavailability); *see United States* v. *Generix Drug Corp.*, 654 F. 2d 1114 (5th Cir. 1981) (*Generix*), *cert. granted*, 50 U.S.L.W. 3695 (Mar. 1, 1982); *Premo Pharmaceutical*

Laboratories, Inc. v. *United States*, 629 F. 2d 795 (2d Cir. 1980) (*Premo I*); *United States* v. *Articles of Drug* (*Lannett Co.*), 585 F. 2d 575 (3d Cir. 1978) (*Lannett*); *see also Pharmadyne Laboratories, Inc.* v. *Kennedy*, 466 F. Supp. 100, 103 (D.N.J.) (*Pharmadyne*), *aff'd on other grounds*, 596 F. 2d 568 (3d Cir. 1979).

The government's basic position in the present case, and in the above cited cases, all of which involve generic drugs, is that because of many factors, particularly the manufacturing process and choice of inactive ingredients, may affect a generic drug's bioavailability and thus its bioequivalence to its pioneer drug, the generic drug is a "new drug" (or "new animal drug") and thus subject to premarketing clearance by the FDA, even though the pioneer drug has already been approved by the FDA. Not surprisingly, the manufacturers of generic drugs oppose the FDA's position. Basically the position of the manufacturers is that because the generic drug contains the same *active* ingredient as the FDA-approved pioneer drug, the generic drug is not a "new drug" (or "new animal drug") and thus not subject to FDA premarketing clearance. The manufacturers argue that bioavailability and bioequivalence are not relevant to the question of "new drug" (or "new animal drug") status. Two circuit courts have addressed this issue; the Second Circuit has essentially agreed with the government's position, *see Premo I*, 629 F. 2d 795; the Fifth Circuit has essentially agreed with the manufacturers' position, *see Generix*, 654 F. 2d 1114.

The present action began in July 1979 when the government filed a complaint in district court seeking condemnation and seizure of undetermined quantities of Equidantin and materials used in its manufacture. The government argued that Equidantin was an adulterated drug within the

meaning of 21 U.S.C. § 351(a)(5)[2] and as such subject to seizure under 21 U.S.C. § 334(a)(1).[3] The government's characterization of Equidantin as an adulterated drug depended upon Equidantin's status as a "new animal drug" within the meaning of 21 U.S.C. § 321(w).[4] Because a new

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2. 21 U.S.C. § 351(a)(5) provides: "A drug . . . shall be deemed to be adulterated— . . . (5) if it is a new animal drug which is unsafe within the meaning of section 360b of this title . . . ."

3. 21 U.S.C. § 334(a)(1) provides in part:

> Any article of . . . drug . . . that is adulterated . . . when introduced into or while in interstate commerce or while held for sale (whether or not the first sale) after shipment in interstate commerce . . . shall be liable to be proceeded against while in interstate commerce, or at any time thereafter, on libel of information and condemned in any district court of the United States . . . within the jurisdiction of which the article is found. . . .

4. 21 U.S.C. § 321(w) provides in part:

> The term "new animal drug" means any drug intended for use for animals other than man, . . .—
>
> (1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; . . . or
>
> (2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions. . . .

animal drug cannot be marketed without an FDA-approved "new animal drug application" or an abbreviated new animal drug application, 21 U.S.C. § 360b(b),[5] and it was not disputed that there was no FDA-approved new animal drug application on file for Equidantin, the government argued that Equidantin was "unsafe" under 21 U.S.C. § 360b(a)(1)(A)[6] and therefore "adulterated" under 21 U.S.C. § 351(a)(5). The district court issued the warrant and the United States Marshal seized approximately 86 quarts of Equidantin, approximately 410 gallons of in-process drug product, 3.4 kilograms of bulk nitrofurantoin powder, and labels and accompanying materials.

Performance intervened in the condemnation action and filed a claim to the seized items. Performance did not dispute that FDA approval is the prerequisite to marketing a new animal drug, but argued that Equidantin is not a new animal drug within the meaning of 21 U.S.C. § 321(w) because it is generally recognized as safe and effective and

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5. 21 U.S.C. § 360b(b) provides in part: "Any person may file with the Secretary an application with respect to any intended use or uses of a new animal drug." The section further describes the contents of a new animal drug application (reports of investigations, listing of components, statement of composition, description of methods and facilities and controls used in manufacture, processing and packing, samples of the new animal drug, samples of labeling, etc.).

6. 21 U.S.C. § 360b (a)(1)(A) provides: "A new animal drug shall, in respect to any particular use or intended use of such drug, be deemed unsafe for the purposes of section 351(a)(5) . . . of this title unless—(A) there is in effect an approval of an application filed pursuant to subsection (b) of this section with respect to such use or intended use of such drug. . . ."

because it is a generic or copy of Dantafur, the FDA-approved pioneer drug.

Following a bench trial in which both sides presented expert testimony, the district court found that Equidantin was a new animal drug within the meaning of 21 U.S.C. § 321(w) because it was not generally recognized among qualified experts as safe and effective. *United States* v. *Undetermined Quantities of Various Articles of Drug (Equidantin Nitrofurantoin Suspension)*, No. 79-0913-C (C) (E.D. Mo. May 29, 1981) (slip op. at 5-6). The district court also found that FDA approval of Dantafur did not constitute general recognition among qualified experts that either Dantafur or Equidantin was safe and effective within the meaning of 21 U.S.C. § 321(w) and, further, that even if Dantafur was generally recognized among qualified experts as safe and effective, Equidantin would not be exempt from FDA premarketing clearance as a new animal drug because the two drugs' inactive ingredients and manufacturing processes differed. *Id.* at 5. The district court then ordered the seized items destroyed, but later stayed that order pending appeal.

The issue in this case is thus whether Equidantin is a "new animal drug" within the meaning of 21 U.S.C. § 321 (w). The scope of FDA regulation depends upon the statutory definitions. A brief outline of the history of FDA regulation will provide a background and perspective to our discussion. *See Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *USV Pharmaceutical Corp.* v. *Weinberger*, 412 U.S. 655 (1973); *see generally* Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Geo. L.J. 185 (1971). It should also be noted that the analysis followed in the cases is the same for human and animal drugs. *United States* v. *Naremco, Inc.*, 553 F. 2d

1138, 1142 n.5 (8th Cir. 1977), *citing United States* v. *Articles of Food and Drug (Coli-Trol 80 Medicated)*, 372 F. Supp. 915, 921 (N.D. Ga. 1974), *aff'd*, 518 F. 2d 743 (5th Cir. 1975).

> The Food and Drug Act of 1906, ch. 3915, 34 Stat. 768, was the first legislation of national scope directed at the regulation of drug products. The Act set standards of purity for drugs sold in the United States and required accurate labeling of the drugs' contents. *Id.* §§ 1, 2, 7. The Act also made unlawful the marketing of adulterated or misbranded drugs and provided for removal of such drugs from the market through libel actions. *Id.* § 2. There were, however, no provisions regulating false claims of efficacy until the Food and Drug Act of 1906 was amended in 1912 to declare misbranded drugs that were not effective for use under the conditions for which they were recommended.
>
> The greatest defect in the Act, however, was its failure to provide any mechanism for premarketing agency clearance. It was impossible to prevent an unsafe or ineffective drug from reaching the market. In 1938 the "wonder drug" Elixer Sulfanilamide," a solution based on diethylene glycol and . . . a presumed harmless, inert solvent ingredient, went on the market. Apparently, no tests for toxicity were performed prior to marketing; and almost one hundred people died before the drug could be withdrawn.
>
> This Sulfanilamide tragedy led to the Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. §§ 301-392 (1976 & Supp. I 1977) (amended 1962), with provisions for premarketing review of new drugs. This review, however, was directed solely to assuring drug-product safety. It was not until the Act was amended in 1962 that the definition of "new drug" was enlarged to include drugs not generally recognized as safe and effective.

> The 1962 amendments changed the data-reporting requirements of the "new drug" procedure to require submission of data showing efficacy and, in place of automatic approval of [new drug applications] not disapproved, the procedure under the 1938 Act, the 1962 amendments required positive agency approval to make [a new drug application] effective.

Premo II, 511 F. Supp. at 962 (footnote omitted).

> The new effectiveness requirement of the 1962 legislation was made retroactive to all drugs which had been the subject of new drug applications under the 1938 statute. Thus, it applied to all drugs which previously had secured FDA pre-marketing approvals. . .
>
> The FDA, recognizing that a transitional period would be necessary to review all drug products affected by the 1962 amendments, granted a two-year grace period before revoking any [new drug applications] given under the 1938 Act. This period of time was to be used to assess the evidence of "effectiveness" of approved drug products. Two years proved to be insufficient time to permit the FDA to evaluate the status of all drugs potentially made "new drugs" by the 1962 amendments. Therefore, in order to expedite the task of evaluation, the FDA arranged with the National Academy of Sciences—National Research Council ("NAS-NRC") to have them review all qualities of the potential "new drugs."
>
> NAS-NRC under took a study of some 4,000 drug formulations for the express purpose of assessing the efficiency of the product. This study, known as the Drug Efficacy Study, was submitted to the FDA for evaluation; the FDA retained authority to accept or reject the findings of NAS-NRC. As a result of the NAS-NRC findings, the FDA set forth in the Federal Register its conclusions and assessment ("Drug Efficacy Study Implementation" or "DESI" Notices) of whether a drug could be considered "effective" for

> use as required by the 1962 amendments to the [1938] Drug Act.

Lannett, 585 F. 2d at 577-78; *see also Note*, 60 Geo. L. J. at 207-14.

As noted earlier, the regulatory scheme for human and animal drugs is basically the same. In 1968 the animal drug provisions were placed in a separate section of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 360b. Animal Drug Amendments of 1968, Pub. L. No. 90-399, 82 Stat. 343 (1968). The definition of "new animal drug" in 21 U.S.C. § 321(w) and the requirement of premarketing clearance by the FDA of new animal drugs under 21 U.S.C. § 360b(b) are essentially the same as the "new drug" definition in 21 U.S.C. § 321(p) and the premarketing clearance provision in 21 U.S.C. § 355(b), (d).

> Under § 505 of the Act, 21 U.S.C. § 355, no person may market a new drug unless he files with the FDA a new drug application (NDA) demonstrating that the drug is both safe and effective for which it is intended and obtains FDA approval. Normally the applicant furnishes controlled chemical tests and investigations showing that the product is safe and effective, 21 U.S.C. § 355(d). But where the drug product is claimed to be a copy [or generic version] of one already approved by the FDA on the basis of such submissions—sometimes called a "me-too" drug—the applicant may file with the FDA an "abbreviated new drug application" (ANDA), which relies upon the safety and effectiveness tests conducted with respect to the FDA-approved drug (sometimes called the "pioneer drug"). The FDA will only approve an ANDA, however, where the "me-too" drug product is shown to be the therapeutic equivalent of the pioneer and safe and effective in accordance with 21 U.S.C. § 355(d).

Premo I, 629 F. 2d at 798-99; *see also Hoffmann-LaRoche, Inc.* v. *Weinberger*, 425 F. Supp. 890 (D.D.C. 1975). *But cf. Generix*, 654 F. 2d at 1117 n.4 (criticizing *Hoffmann-LaRoche*). As with human drugs, manufacturers of generic animal drugs may rely upon the safety and effectiveness data developed for the pioneer drug and file abbreviated new animal drug applications supported by bioavailability studies.

For reversal Performance argues that the government failed to establish that Equidantin is a new animal drug within the meaning of 21 U.S.C. § 321(w). Performance attacks the credibility of the government expert witnesses on the grounds that they lacked qualifications, had no personal clinical experience with nitrofurantoin suspensions, and did not know that Dantafur had been found "effective" by the NAS-NRC in the Drug Efficacy Study. Dantafur was reviewed by NAS-NRC in the Drug Efficacy Study and was found "probably effective" for the treatment of race track cough and equine urinary infections. 35 Fed. Reg. 12792 (1970). In 1977 a supplemental new animal drug application was approved by the FDA finding Dantafur "effective" for the treatment of race track cough and equine urinary infections. *See* 42 Fed. Reg. 19143 (1977), *codified in* 21 C.F.R. § 520.1560a (1981). There is no approved new animal drug application, abbreviated new animal drug application or exemption for investigational use on file for Equidantin.

> Title 21 U.S.C. § 321(w) defines "new animal drug" as any drug intended for use for animals other than man. . . .—
>
> (1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal

> drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; . . . or
>
> (2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions. . . .

Unless an animal drug is generally recognized among qualified experts as safe and effective for its intended uses and has been used to a material extent or for a material time, the drug is a new animal drug and subject to FDA premarketing clearance. *See Premo I*, 629 F. 2d at 801-02.

> Congress' exclusion of "generally recognized" drug products from the definition of a "new drug" is a very narrow one, which is not intended to permit a pharmaceutical manufacturer to substitute its opinion regarding the safety or effectiveness of a drug for that of the FDA, the publicly recognized repository of expertise in such matters, or to require the court to develop its own body of scientific knowledge in substitution for that of the FDA.

Id. at 802.

> Thus, while a district court certainly is empowered to adjudicate the "new drug" status of a given drug product, inquiry is limited to the question of "general recognition." A district court is not empowered to evaluate the actual safety and effectiveness of a drug product. That determination is committed to the FDA due to its superior access to technical expertise.

United States v. *Articles of Drug (Hormonin)*, 498 F. Supp. 424, 431 (D.N.J. 1980) (citations omitted); *see also Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645,

653-54 (1973); *AMP, Inc.* v. *Gardner*, 389 F. 2d 825, 831 (2d Cir.), *cert. denied*, 393 U.S. 825 (1968). *Cf. United States* v. *Alcon Laboratories*, 636 F. 2d 876, 888 (1st Cir. 1980) ("Jurisdiction over the new drug issue is shared by the FDA . . . and the federal district courts. . . . [D]eference to an agency's primary jurisdiction makes little sense in the context of an enforcement proceeding initiated by the agency."), *cert. denied*, 451 U.S. 1017 (1981); *accord, Premo I*, 629 F. 2d at 801.

Thus, "the purpose of the normal inquiry [into whether a drug is generally recognized among qualified experts as safe and effective for its intended uses] is not to determine safety and effectiveness at all, but to ascertain the drug's general reputation in the scientific community for such characteristics." *United States* v. *Articles of Food and Drug (Coli-Trol 80 Medicated)*, 372 F. Supp. at 920; *see Premo I*, 629 F. 2d at 803-04 (cases cited therein).

> Either a genuine dispute concerning the safety and effectiveness of a drug product or unawareness of the drug product among qualified experts precludes a finding of "general recognition" for purposes of 21 U.S.C. § 321(p) [for human drugs or § 321(w) for animal drugs]. Such an expert consensus as to "general recognition" must be founded upon "substantial evidence" as that term is defined in 21 U.S.C. § 355(d) [for human drugs and § 360b(d)(3) for animal drugs]. Thus, "general recognition" among experts must be based upon "'adequate and well-controlled investigations,'" as well as publication in scientific literature. "Anecdotal evidence," *i.e.*, testimony of physicians unsupported by controlled investigation or scientific publication, does not constitute "substantial evidence." The mere fact that a drug product has been marketed for an extended period does not preclude a finding of "new drug" status.

United States v. *Articles of Drug* (*Hormonin*), 498 F. Supp. at 431-32 (footnote and citations omitted); *see Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. at 629, 630, 632; *Premo I*, 629 F. 2d at 803-04; *United States* v. *Article of Drug* (*Furestrol*), 294 F. Supp. 1307, 1311 (N.D. Ga. 1968), *aff'd*, 415 F. 2d 390 (5th Cir. 1969).

The government's expert witnesses, Dr. Gary Koritz and Dr. Nicholas Booth, were extremely well qualified; both are veterinarians and university professors, specialists in veterinary pharmacology, experienced in research and widely published. Both testified that nitrofurantoin in general and Equidantin in particular are not generally recognized among qualified experts as safe and effective to treat race track cough or equine urinary tract infections. Both were aware of the publication of the DESI Notice for Dantafur, but expressed reservations about the validity of the supporting scientific data, and disagreed with the evaluation of effectiveness in the DESI Notice on the merits. Both further testified that, as was admitted by Performance, no completed clinical studies on the safety or efficacy of Equidantin have been published (apparently a bioavailability study is now in progress); that the limited published data available on the use of nitrofurantoin in horses did not involve Equidantin (the experts also questioned the scientific design of these studies); and that neither had any knowledge of Equidantin before preparing for the present case.

Another government expert witness, Dr. Marvin Meyer, a professor of pharmacy and specialist in biopharmaceutics (the study of factors that affect the absorption, metabolism, distribution, and excretion of drugs), testified at some length about bioavailability. Dr. Meyers testified that bioavailability was important in evaluating the efficacy of

nearly all drug products, including suspensions; that differences or changes in bioavailability may affect a drug's therapeutic value; and that many factors can affect bioavailability, including variations in product formation, particularly the suspension medium and the crystal size of the active ingredient. *See Premo II*, 511 F. Supp. at 962-65.

Performance presented the testimony of two professors of pharmacy who testified that the inactive ingredients used in the manufacture of Equidantin are generally recognized as safe for use in pharmaceutical preparations. Another witness, a practicing veterinarian, testified that he prescribed Equidantin and had found it safe and effective. None of Performance's witnesses, however, testified that either nitrofurantoin or Equidantin was generally recognized among qualified experts as safe and effective for its intended uses. The practicing veterinarian's testimony was not supported by clinical studies or published data and was clearly anecdotal in character.

After reviewing the testimony under the standards set forth above, we can find no error in the district court's finding that Equidantin is not generally recognized among qualified experts as safe and effective for its intended uses and therefore, in the absence of general recognition, a new animal drug within the meaning of 21 U.S.C. § 321(w). Not only were the government expert witnesses unaware of Equidantin before preparing to testify in the present case, there was at best a sharp difference of opinion among the experts; there was certainly no general consensus of expert opinion in favor of Equidantin. Nor was there any published scientific literature or well-controlled clinical investigations of Equidantin. *See United States* v. *Articles of Drug (Hormonin)*, 498 F. Supp. at 431-32.

Performance next argues that Equidantin is not a new animal drug within the meaning of 21 U.S.C. § 321(w) because Equidantin is a generic version or copy of an FDA approved drug. Performance argues that because Dantafur has been approved by the FDA (in the DESI Notice) and because Dantafur and Equidantin contain the same active ingredient (nitrofurantoin) in the same concentration per dosage unit, Equidantin is not a new animal drug within the meaning of the statute. This argument is incorrect; FDA approval, that is, agency recognition of actual safety and effectiveness, must not be confused with general recognition in the scientific community of safety and effectiveness. As discussed earlier, only general recognition plus material use can exempt a drug from new drug status and FDA premarketing clearance. As noted by the Supreme Court in *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, "the Act is designed so that drugs on the market . . . will have mustered the requisite scientifically reliable evidence of effectiveness long before they are in a position to drop out of active regulation by ceasing to be a 'new drug.' " 412 U.S. at 631; *see also Premo I*, 629 F. 2d at 803-04. FDA approval is the threshold determination required before the manufacturer can market the drug; it does not exempt the drug from new drug status. Prior FDA approval of Dantafur means only that, if Performance should apply for FDA approval of Equidantin, Performance can rely on the safety and effectiveness data submitted for Dantafur because Dantafur and Equidantin contain the same active ingredient and need only add bioavailability studies to complete its application.

Moreover, the government in the present case showed that nitrofurantoin was not generally recognized among qualified experts as safe and effective. Therefore, even

assuming for purposes of argument that the statutory definition of new drug refers only to the active ingredient, Eqvidantin would not be exempt from new drug status because its active ingredient, nitrofurantoin, is not generally recognized among qualified experts as safe and effective and is therefore a "new drug." *Compare Generix*, 654 F. 2d at 1115-20 (the term "new drug" as used in 21 U.S.C. § 321(p) applies only to the active ingredients of a drug product), *with Premo I*, 629 F. 2d at 801 (a drug product is a "new drug" unless generally recognized among qualified experts as safe and effective); *Premo II*, 511 F. Supp. at 968-73; *and Pharmadyne*, 466 F. Supp. at 103-04. Because the government in the present case showed that neither the pioneer drug (Dantafur) nor the active ingredient (nitrofurantoin) was generally recognized among qualified experts as safe and effective, we need not address whether the term "drug" as used in 21 U.S.C. § 321(p), (w) refers only to the active ingredient in a drug product; if it does, whether general recognition of the pioneer drug will remove any generic copy from new drug status; or if it does not, whether general recognition of the pioneer drug will remove an exact generic copy (identical active and inactive ingredients and manufacturing processes) from new drug status.

Accordingly, the judgment of the district court is affirmed.

A true copy.

ATTEST:

ROBERT D. ST. ORAIN,
CLERK, U.S. COURT OF APPEALS,
EIGHTH CIRCUIT

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

UNITED STATES OF AMERICA,
Plaintiff,

v.

Undetermined quantities of various articles of drug . . .

EQUIDANTIN NITROFURANTOIN SUSPENSION . . .,
Defendant.

No. 79-0913-C (C)

JUDGMENT

Findings Of Fact and Conclusions Of Law dated this date are hereby incorporated into and made a part of this judgment.

IT IS HEREBY ORDERED, ADJUDGED AND DECREED that the articles of drug and labeling under seizure in this action are condemned as adulterated pursuant to 21 U.S.C. § 334. The United States Attorney of this District shall submit within ten days a proposed order of disposition of such articles. Claimant Performance Products, Inc. shall then have ten days to respond to the proposed disposition of the articles.

All costs are assessed against claimant Performance Products, Inc.

DATED this 29th day of May, 1981.

JAMES H. MEREDITH,
UNITED STATES DISTRICT JUDGE

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

UNITED STATES OF AMERICA,
Plaintiff,

v.

Undetermined quantities of various articles of drug . . .

EQUIDANTIN NITROFURANTOIN SUSPENSION . . .,
Defendant.

No. 79-0913-C (C)

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This matter is before the Court for a decision on the merits after trial to the Court. This is a civil *in rem* action commenced July 25, 1979 for the condemnation as adulterated of certain articles of animal drug, Equidantin brand of nitrofurantoin suspension ("Equidantin"), and components used in the manufacture of Equidantin. It is claimed that these articles are "new animal drugs" which are legally unsafe because no approved application therefor is in effect. The articles were seized and Performance Products, Inc. intervened as claimant.

After consideration of the pleadings, testimony and exhibits introduced at trial, the parties' briefs and the applicable law, the Court makes the following findings of fact and conclusions of law. Any finding of fact equally applicable as a conclusion of law is adopted as such, and conversely, any conclusion of law equally applicable as a finding of fact is so adopted.

Findings of Fact

1. On July 25, 1979, plaintiff United States of America filed a complaint seeking condemnation of undetermined quantities of various articles of drug for animal use, specifically:

A. Finished drug product for animal use, Equidantin brand of nitrofurantoin suspension;

B. In-process drugs for animal use which contain nitrofurantoin that has been shipped in interstate commerce;

C. Bulk nitrofurantoin intended for use in finished drug products which nitrofurantoin has been shipped in interstate commerce; and

D. Labels and accompanying labeling to be used with the aforesaid articles of drug.

2. On August 8, 1979 and September 20, 1979, pursuant to a warrant for arrest *in rem*, the United States Marshal for this District seized the articles complained against, specifically:

A. A total of 86, more or less, 1-quart bottles of finished drug product;

B. 410 gallons, more or less, of in-process drug product;

C. 3.4 kilograms of bulk nitrofurantoin powder; and

D. Labels and accompanying labeling.

3. Thereafter, Performance Products, Inc. ("claimant") intervened and filed a verified claim to the seized articles. In its answer, claimant denied that the articles were adulterated as alleged in the complaint.

4. The bulk nitrofurantoin power seized was intended for use in the manufacture of the finished drug products and in-process drug products under seizure.

5. The bulk nitrofurantoin powder seized was shipped to Performance Products from outside of the State of Missouri.

6. The articles under seizure were being held by claimant, a veterinary drug manufacturer, at claimant's manufacturing facility at 1627 Locust Street, St. Louis, Missouri, for distribution to claimant's customers in the normal course of claimant's business.

7. According to the labeling and package inserts seized, the product is for use in the treatment of equine tracheopharyngitis and bacterial infections of the urinary tract in equines.

8. The labeling and package inserts stating that the product is to be used for treatment of equine tracheopharyngitis and bacterial infections of the urinary tract in equines are intended to accompany each of the finished products.

9. The articles under seizure are intended for use in the cure, mitigation, and treatment of disease in animals and are intended to affect the function of the body in animals.

10. There is no approved New Animal Drug Application (NADA) filed pursuant to 21 U.S.C. § 360b(b) in effect for Equidantin brand of nitrofurantoin suspension.

11. At the time of manufacture of the products under seizure, there was no Notice of Claimed Investigational New Animal Drug (INAD) exemption on file with the Food and Drug Administration that permitted the investigational use of Equidantin by claimant.

12. Equidantin brand of nitrofurantoin suspension has not been the subject of any well-controlled investigations, including field investigations, that would establish it to be safe and effective for its intended uses.

13. There is no substantial evidence in the form of published scientific literature that establishes that Equidantin is safe and effective for its intended uses.

14. Equidantin is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.

15. As part of the Drug Efficacy Study Implementation, the National Academy Of Sciences/National Research Council ("NAS/NRC") reviewed the efficacy of Dantafur brand of nitrofurantoin suspension. The NAS/NRC findings were published in the Federal Register, 35 Fed. Reg. 12792 (August 12, 1970).

16. The NAS/NRC found Dantafur brand of nitrofurantoin supension to be "probably effective" for, *inter alia*, equine tracheopharyngitis and bacterial infections of the urinary tract in equines.

Conclusions of Law

1. This Court has jurisdiction herein pursuant to 21 U.S.C. § 334 and 28 U.S.C. § 1345.

2. The finished products and in-process products under seizure are "drugs" within the meaning of 21 U.S.C. § 321(g)(1)(B) and (C) because they are articles intended for use in the cure, mitigation, and treatment of disease in animals and are intended to affect the function of the body of animals.

3. The bulk nitrofurantoin under seizure is a "drug" within the meaning of 21 U.S.C. § 321(g)(1)(D) because it is intended for use as a component of a drug.

4. The bulk nitrofurantoin powder used to compound the finished and in-process products under seizure and the bulk nitrofurantoin under seizure were shipped in interstate commerce into the state of Missouri from outside Missouri. Therefore, the seized articles are within the jurisdiction of this Court, 21 U.S.C. § 334.

5. At the time of the filing of the complaint and of seizure, the seized articles of drug were being held for sale within the meaning of 21 U.S.C. § 334.

6. The bottle labels and package inserts seized are "labeling" within the meaning of 21 U.S.C. § 321m(1) and (2).

7. The NAS/NRC finding that Dantafur brand of nitrofurantoin suspension is "probably effective" for treatment of equine tracheopharyngitis and bacterial infections of the urinary tract in equines does not constitute general recognition by qualified experts of the safety and effectiveness of nitrofurantoin suspension, including Dantafur, for those indications within the meaning of 21 U.S.C. § 321(w).

8. Even if the Dantafur brand of nitrofurantoin suspension was generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for its intended uses, this would not exempt Equidantin brand of nitrofurantoin suspension from the New Animal Drug Application procedures of 21 U.S.C. § 360b because of the potential differences in manufacturing processes and inactive ingredients between the two drugs. *Premo Pharmaceutical Laboratories, Inc.* v. *United States,* 629 F. 2d 795 (2d Cir. 1980); *United States* v. *An Article Of Drug,* 362 F. Supp. 424 (S.D. Cal. 1973), *aff'd,* 513 F. 2d 1127 (9th Cir. 1975); *United States* v. *Premo Pharmaceutical Labora-*

tories, Inc., No. 80-699 (D. N.J. filed January 20, 1981); *Pharmadyne Laboratories, Inc.* v. *Kennedy*, 466 F. Supp. 100 (D. N.J. 1979).

9. Equidantin is a "new animal drug" within the meaning of 21 U.S.C. § 321(w) because it is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use in the treatment of equine tracheopharyngitis or bacterial infections of the urinary tract in equines.

10. Equidantin is an unsafe new animal drug within the meaning of 21 U.S.C. § 360b(a)(1)(A) because no approval of an application filed pursuant to 21 U.S.C. § 360b(b) is in effect.

11. At the time of manufacture, Equidantin was not exempt from the requirement of 21 U.S.C. § 360b(b) because there was no Notice of Claimed Investigational New Animal Drug exemption in effect permitting the investigational use of this product.

12. The Equidantin nitrofurantoin suspension under seizure is adulterated within the meaning of 21 U.S.C. § 351(a)(5), as a matter of law, because it is a new animal drug that is unsafe within the meaning of 21 U.S.C. § 360b.

13. The articles of drug under seizure are adulterated while held for sale after shipment in interstate commerce, and therefore, are condemned pursuant to 21 U.S.C. § 334.

14. The articles and labeling under seizure in this action may be disposed of by Order of this Court pursuant to 21 U.S.C. § 334(d).

DATED this 29th day of May, 1981.

JAMES H. MEREDITH,
UNITED STATES DISTRICT JUDGE

FEDERAL FOOD, DRUG, AND COSMETIC ACT
21 U.S.C. § (p) (1976)

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall be deemed to be a "new drug" if at any time prior to the enactment of this Act [June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

FEDERAL FOOD, DRUG, AND COSMETIC ACT
21 U.S.C. § 321(w) (1976)

(w) The term "new animal drug" means any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed—

(1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; except that such a drug not so recognized shall not be deemed to be a "new animal drug" if at any time prior to June 25, 1938, it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions; or

(3) which drug is composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin, or any derivative thereof, except when there is in effect a published order of the Secretary declaring such drug not to be a new animal drug on the grounds that (A) the requirement of certification of batches of such drug, as provided for in section 512(n), is not necessary to insure that the objectives specified in paragraph (3) thereof are achieved and (B) that neither subparagraph (1) nor (2) of this paragraph (w) applies to such drug.

FILED
SEP 28 1982
ALEXANDER L. STEVAS

No. 81-2402

In the Supreme Court of the United States

OCTOBER TERM, 1982

UNDETERMINED QUANTITIES OF VARIOUS ARTICLES OF DRUG . . . EQUIDANTIN . . ., PERFORMANCE PRODUCTS, INC., PETITIONER

v.

UNITED STATES OF AMERICA

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE EIGHTH CIRCUIT

MEMORANDUM FOR THE UNITED STATES IN OPPOSITION

REX E. LEE
Solicitor General
Department of Justice
Washington, D.C. 20530
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TABLE OF AUTHORITIES

Page

Cases:

Berenyi v. *Immigration Director*, 385 U.S. 630 6

International Brotherhood of Electrical Workers v. *Foust*, 442 U.S. 42 6

Premo Pharmaceutical Laboratories, Inc. v. *United States*, 629 F. 2d 795 3

United States v. *41 Cases More or Less Naremco, Inc.*, 420 F. 2d 1126 5

United States v. *Generix Drug Corp.*, 654 F. 2d 1114, cert. granted, No. 81-1222 (Mar. 1, 1982) 3, 4

United States v. *Johnston*, 268 U.S. 220 6

USV Pharmaceutical Corp. v. *Weinberger*, 412 U.S. 655 5

Weinberger v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 5

Weinberger v. *Hynson, Westcott & Dunning*, 412 U.S. 609 5

Statutes and regulations:

Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.* 2

21 U.S.C. 321(w) 2, 3
21 U.S.C. 321(w)(1) 2
21 U.S.C. 334(a)(1) 2
21 U.S.C. 351(a)(5) 2
21 U.S.C. 360b(b) 1, 2

Page

Statutes and regulations—Continued:

21 U.S.C. 360b(j) 1
21 U.S.C. 360b(a)(1)(A) 2
Pub. L. No. 87-781, 76 Stat. 780 2
21 C.F.R. 520.1560 (1981) 2
21 C.F.R. 520.1560a (1981) 2

Miscellaneous:

35 Fed. Reg. 12792 (1970) 2
42 Fed. Reg. 19143 (1977) 2

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v.

UNITED STATES OF AMERICA

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE EIGHTH CIRCUIT

MEMORANDUM FOR THE UNITED STATES IN OPPOSITION

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1. Petitioner Performance Products, Inc. (Performance) manufactures the animal drug Equidantin (Pet. App. A2), which is labeled for use in the treatment of two equine ailments (*ibid.*). Although Equidantin has been marketed by Performance since 1970, there is no new animal drug application (NADA) for Equidantin approved by the Food and Drug Administration (FDA). Nor was there at the time of Equidantin's manufacture an investigational new animal drug exemption (INAD) on file with FDA permitting its investigational use (*id.* at A6, A21; see 21 U.S.C. 360b(b) and (j)). It is through the approval of a NADA by the FDA that a veterinary drug that is not generally recognized by experts as safe and effective for its intended uses can be marketed (Pet. App. A5-A6). In fact, there have been no well-controlled clinical studies that establish that Equidantin is safe and effective for its labeled uses (Pet. App. A15).

Equidantin contains one active ingredient, nitrofurantoin, which is also the active ingredient of the FDA-approved product Dantafur (*id.* at A2).[1]

2. In July 1979, the government filed a complaint seeking, *inter alia*, seizure and condemnation of quantities of Equidantin on the ground that it was a new animal drug, 21 U.S.C. 321(w), that lacked FDA approval (21 U.S.C. 360b(b)), and thus was unsafe within the meaning of 21 U.S.C. 360b(a)(1)(A) (*id.* at A-6). As an unsafe new animal drug, Equidantin was adulterated, as a matter of law, 21 U.S.C. 351(a)(5), and, accordingly, subject to seizure and condemnation, 21 U.S.C. 334(a)(1) (*id.* at A4-A5). Petitioner intervened in the seizure action as claimant and contended that Equidantin was not a new animal drug.

Following a bench trial, the district court found that Equidantin was not generally recognized among qualified experts as safe and effective for its labeled uses (Pet. App. A22, A24), see 21 U.S.C. 321(w)(1), and thus concluded that Equidantin was an unapproved new animal drug (Pet. App. A24). The court also found that Equidantin would not be exempt from the NADA procedures even if Dantafur were generally recognized as safe and effective (*id.* at A23). The seized items were condemned but destruction was stayed pending appeal (*id.* at A7).

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[1]Dantafur is labeled for the same two uses in horses as Equidantin (see *id.* at A2, A11). Unlike Equidantin, however, Dantafur was reviewed by the National Academy of Sciences/National Research Counsel as part of the Drug Efficacy Study Implementation (DESI) review following the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, Pub. L. No. 87-781, 76 Stat. 780, and found "probably effective." Pet. App. A11; 35 Fed. Reg. 12792 (1970). FDA approved a supplemental NADA for Dantafur in 1977. Pet. App. A11; 42 Fed. Reg. 19143 (1977), codified in 21 C.F.R. 520.1560 and 520.1560a (1981). While a dosage unit of Equidantin and Dantafur contain the same quantity of nitrofurantoin, the two drug products have different inactive ingredients. Pet. App. A2.

The court of appeals unanimously affirmed (Pet. App. A17). After a careful review of the record, the court found that neither Equidantin nor its active ingredient, nitrofurantoin, was generally recognized among qualified experts as safe and effective for its intended uses (*id.* at A15, A17).[2] The court rejected Performance's argument that prior FDA approval of Dantafur exempted Equidantin from new animal drug status, noting that petitioner had wrongly confused "agency recognition of actual safety and effectiveness [by approval of the Dantafur NADA], * * * with general recognition in the scientific community of safety and effectiveness" (*id.* at A16).

In addition, the court expressly concluded (Pet. App. A17) that the record in this case presented no occasion for deciding whether the term "drug" in 21 U.S.C. 321(w) refers to a drug product or only to its active ingredient.[3] Because neither the product nor the active ingredient is generally recognized by experts as safe and effective, Equidantin remains subject to condemnation as an unapproved new animal drug no matter how that legal issue is resolved.

3. The decision of the court of appeals is correct. It does not conflict with a decision of any other court of appeals and does not raise any issue warranting review by this Court. Petitioner contends that the court below rejected the analysis of the court of appeals in *Generix*, and "implicitly adopted" the view "that bioavailability is an attribute of a 'new animal drug' by its acceptance of and reliance upon the

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[2]The court observed that "[n]one of [petitioner's] witnesses" had testified to the contrary (Pet. App. A15).

[3]This is an issue on which the courts of appeals, in the context of new human drugs, are in conflict. Compare *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F. 2d 795 (2d Cir. 1980), with *United States* v. *Generix Drug Corp.*, 654 F. 2d 1114 (5th Cir. 1981), cert. granted, No. 81-1222 (Mar. 1, 1982) ("*Generix*").

expert testimony presented by the Government" (Pet. 6). But, because of the factual record below, this case does not present the same legal issue that is before this Court in *Generix*. Moreover, petitioner's argument ignores the rationale of the court below.

Respondents in the *Generix* case contend that their "products do not require premarket clearance because their active ingredients are generally recognized as safe and effective" (Resp. Br. 11).[4] Their merits brief expressly disclaims reliance on the fact that FDA has approved new drug applications for other drug products containing the same active ingredients as their products (*ibid.*).

Unlike respondents in *Generix*, petitioner in this case cannot argue that its drug is exempted from premarketing clearance because its active ingredient, nitrofurantoin, is generally recognized as safe and effective. The court of appeals found, and the record below establishes, to the contrary, that nitrofurantoin is not generally recognized by experts as safe and effective (Pet. App. A16-A17). Thus, the court of appeals reasoned that, even if, as respondents contend in *Generix* (Resp. Br. 13), "the statutory definition of new [animal] drug refers only to the active ingredient, Equidantin would not be exempt from new [animal] drug status because its active ingredient, nitrofurantoin, is not generally recognized among qualified experts as safe and effective and is therefore a 'new [animal] drug' " (Pet. App. A17). Accordingly, however *Generix* is decided, Equidantin will remain subject to condemnation.

Petitioner contends that the courts below erred by relying on bioavailability data which, it argues, are irrelevant in determining whether a drug is a "new animal drug" (Pet.

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[4] "Resp. Br." refers to the brief for the respondents in *United States* v. *Generix Drug Corporation*, No. 81-1222.

6-8).[5] This contention is not supported by the record. Although the court of appeals summarized all the expert testimony on both sides (Pet. App. A14-A15), it did not rely on the testimony of the government's bioavailability expert. Rather the court's ruling is amply supported by expert testimony based not on bioavailability considerations but on the fact that there are no well controlled studies in horses showing that either nitrofurantoin generally, or Equidantin specifically, is effective in treating the indicated diseases (Pet. App. A14-A15; Tr. 28-31, 34, 36; Booth Dep. 33, 41).[6]

The court of appeals' reliance on this expert opinion accords with the approach that this Court and others have taken in determining whether a drug is generally recognized by qualified experts as safe and effective. For there to be "general recognition" of a drug, there must be, among other things, well-controlled investigations reported in the scientific literature demonstrating the drug's safety and effectiveness for its intended uses. See, *e.g.*, *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973); *Weinberger* v. *Hynson, Westcott & Dunning*, 412 U.S. 609, 629-630, 632 (1973); *United States* v. *41 Cases, More or Less . . . Naremco, Inc.*, 420 F. 2d 1126, 1130 (5th Cir. 1970). Since there are no reliable studies in the scientific literature concerning the use in horses of either nitrofurantoin or Equidantin, the court of appeals correctly concluded

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[5]Petitioner does not challenge the court of appeals' determination that FDA approval of Dantafur, by itself, does not confer general recognition of safety and effectiveness on either its active ingredient, nitrofurantoin, Dantafur itself, or Equidantin. This holding is consistent with prior decisions of this Court (*Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631 (1973); *USV Pharmaceutical Corp.* v. *Weinberger*, 412 U.S. 655, 664 (1973)).

[6]"Tr." refers to the transcript of the district court proceedings. "Booth Dep." refers to the deposition of Dr. Nicholas Booth, introduced into evidence at the trial. Tr. 3.

that these drugs cannot be generally recognized as safe and effective. There is no need for this Court to review a factual determination that is of importance only in this particular case. *United States* v. *Johnston*, 268 U.S. 220, 227 (1925); *Berenyi* v. *Immigration Director*, 385 U.S. 630, 635 (1967); *International Brotherhood of Electrical Workers* v. *Foust*, 442 U.S. 42, 46 n.7 (1979).

It is respectfully submitted that the petition for a writ of certiorari should be denied.

REX E. LEE
Solicitor General

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